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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,403	04/15/2002	Donald Gullberg	000510-010	3147

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,403	GULLBERG, DONALD	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13 and 155* is/are rejected.

7)☒ Claim(s) *22,153 and 154* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/01/06 has been entered.

2. Claims 1-10, 12-13, 15-19, 21-22, 26-27, 29-93, 95-105, 107-112, 114, 117-118, 120, 125, 127-145, 147-148 and 153-155 are pending.

3. Claims 2-10, 12, 15-19, 21, 26, 27, 29-93, 95-105, 107-112, 114, 117, 118, 120, 125, 127-145 and 147-148 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 13, 22 and 153-155 are under consideration in the instant application as they read on a recombinant or isolated integrin subunit α11 having the amino acid sequence encoded by SEQ ID NO: 1, fragments thereof and a composition thereof.

5. Claim 22 is objected to because "said fragment a peptide" is missing a verb after "said fragment".

6. Claims 153-154 are objected to because of the following informalities: the "," after domain is improper and should be deleted.

7. It is noted that Applicant has deleted "β1" in currently amended claim 13 without showing strikethrough. Deleted text must be shown by strikethrough.

8. The amendment filed 5/21/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The preliminary amendment filed on 5/21/05 to replace original figure 8 with the new figure 8 represents a departure from the specification and the claims as originally filed. Applicant points out figure 8 replacement provide simply better quality drawing. However, the specification and the claims as originally filed have no support for the new replacement of original figure 8 with the newly submitted figure 8. It is noted that the arrows pointing to different vertebrae in the newly submitted figure 8.

Applicant is required to cancel the new matter in the response to this Office action.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an isolated integrin subunit α11 having the amino acid sequence of SEQ ID NO: 2 or fragments thereof, wherein the fragments are selected from the group consisting of a peptide consisting of the amino acid sequence from the cytoplasmic domain from amino acid 1165-1188 of SEQ ID NO:2, the amino acid sequence of the extracellular domain from amino acid 804-826 of SEQ ID NO:2, the amino acid of the I-domain from amino acid 159-355 of SEQ ID NO: 2, a composition thereof; a heterodimer comprising α11β1; a composition thereof a fragment consisting of the amino acid sequence KLGFFRSARRRREPGLDPTPKVLE, the extracellular domain consisting of amino acids 804-826 of SEQ ID NO:2, the I-domain consisting of amino acid 159 to 355 of SEQ ID NO:2 and a composition thereof, does not reasonably provide **enablement** for a recombinant integrin subunit α11 "comprising" fragments of SEQ ID NO: 2 in claim 1, a recombinant integrin heterodimer comprising a subunit α11 according to claim 1 and any "subunit" in claim 13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Actions mailed 10/21/04 and 5/19/05.

Further, claim 13 recites that the integrin heterodimer comprising α11 and any "subunit", however, the specification on page 24, lines 14-35 discloses that an antibody which was raised to the cytoplasmic tail of the integrin α11 chain immuoprecipitated a 145 KDa α11 band associated with a 115 KDa β1 band in SDS-PAGE under non-reducing conditions. Further, the specification on page 25, line 3-11 discloses that α11 is associated with the β1 subunit. Besides β1, the specification falls to provide α11 heterodimer comprising any subunit.

Besides SEQ ID NO: 2, the specification fails to provide any integrin subunit α11 "comprising" the recited fragments in claim 1.

The term "comprising" in claims 1 and 154 is open ended and extend the fragment peptide to include additional unspecified amino acids on either or both sides of I-domain outside 159-355 amino acids. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to the collagen type I binding and that the relationship between the peptide and its activity was not well understood. It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of fragments of integrin subunit α11 that binds collagen type I. Without sufficient guidance, the changes which can be made in the structure of "fragment" and still provide collagen type I

binding activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 11/21/05, have been fully considered, but have not been found persuasive.

Applicant submits that at the time the present application was filed the skilled artisan could readily make the fragment as claims and then test it for collagen type I-binding activity without undue experimentation. Applicant points to the specification which provides detailed comments on testing a peptide fragment for collagen-binding activity by chromatographic means. Applicant contends that the involvement of the I-domain in the collagen-binding activity of integrin α subunits was known at the priority date of the present application. The role of the I-domain in Collagen binding is well recognized, and is discussed in the introduction of the present specification. Applicant concludes that the application as-filed provides clear guidance as to the amino acid sequence requirements to retain collagen-binding activity. Applicant provides a r3eview article by Dickeson&Santoro to support his position. Applicant refers to the statement that experimental techniques for testing ligand binding properties of cell surface receptors were not in routine use at the priority date of the application as filed. Applicant directs the Examiner's attention to Gullberg et al 1999 article as a support for the chromatographic method described in the specification.

However, besides SEQ ID NO: 2, the specification fails to provide any integrin subunit α11 "comprising" the recited fragments in claim 1.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 13, and 155 are rejected under 35 U.S.C. 102(b) as being anticipated by Gullberg *et al* (Dev. Dyn. 204:57-65, 1995) (IDS Ref. No. C2), as is evidenced by Velling *et al* (IDS Ref. No. C5) for the same reasons set forth in the previous Office Action mailed 10/21/04.

Gullberg *et al* teach an isolated integrin subunit αmt obtained from G6 myoblasts and myotubes. Gullberg *et al* teach that αmt is induced upon myogenic differentiation (see abstract). Gullberg et al teaches that under non-reducing conditions β1 associated protein migrated as 145 kD,

wherein under reducing conditions, β1 integrin associated protein migrated in SDS-PAGE as a 155 kD protein (see abstract in particular). Gullberg *et al* teach that αmtβ1 heterodimer (see page 60, 2nd col., 2nd ¶ in particular). While the Gullberg *et al* teachings may be silent as to the "SEQ ID NO: 2" per se; the product is the same as the claimed product. As is evidenced by Velling *et al* that α11 is identical with αmt (see page 25740, 2nd col., end of the 1st ¶ in particular). Applicant's disclosure of SEQ ID NO:2 is mainly further characterization of otherwise old product.

Further, it is noted the referenced αmt integrin subunit "comprises" the recited fragments as recited in claim 1.

The claimed recombinant integrin subunit α11 is the same the referenced integrin subunit αmt (α11) irrespective of how it is made (recombinantly). Further, it has been held that "once a product is fully disclosed in the art, future claims to that same product are precluded, even if that product is claimed as made by a new process." See *In Smithkline Beecham Corp. V. Apotex Corp.*, No . 04-1522 (fed. Cir. February 24, 2006).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 11/21/05, have been fully considered, but have not been found persuasive.

Applicant argues in conjunction with case laws that the Examiner fails to provide evidence to support the assertion that αmt subunit is identical to the α11 subunit. Applicant points that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

Contrary to applicant's assertions the examiner has established a convincing line of reasoning based on established scientific principles and/or legal precedent that αmt and α11 are identical. Applicant's disclosure of SEQ ID NO:2 is mainly further characterization of otherwise old product.

Applicant contends that the comparison between αmt and α11 is not based on the nucleotide and amino acid sequences. Applicant submits that it cannot be concluded with any degree of certainty that the αmt subunit comprises the amino acid sequence of SEQ ID NO: 2. Applicant contends that a conclusion of lack of novelty should only be reached if it can be shown that the Gullerg et al paper comprises an identical sequence to that shown in SEQ ID NO: 2 of the present application (emphasis add by Application).

However, since the office does not have a laboratory to test the reference αmt subunit, it is applicant's burden to show that the reference αmt subunit is not the claimed SEQ ID NO: 2

recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Applicant contends that the amino acid sequence of the αmt subunit is not known. In Gullberg the αmt subunit was identified in human fetal G6 myotubes by immunoprecipitation using antibodies to the β1 integrin subunit. Application points that Gullberg et al article did not extend to the cloning and sequencing of the αmt subunit. Applicant points out that the αmt subunit from human fetal G6 myotubes has never been sequence.

However, it is immaterial whether the αmt from human fetal G6 myotubes is sequenced or not. The disclosure of αmt subunit is identical to α11 anticipates the claimed invention in the absence to evidence to the contrary.

Applicant refers to the attempts by Gullberg et al to clone the αmt gene from human fetal G6 myotubes, but did not succeed. Applicant submits that only when the inventor of the present inventor took the inventive step of using a different cDNA library to that used in the Gullberg, namely a human uterus cDNA library, that he succeed in cloning the α11 gene. Applicant noted that different source material was used for cloning the a11 gene of the present invention from that of Gullberg. Applicant concludes that the αmt subunit disclosed in Gullberg is **not an identical sequence** to that of the α11 subunit the present application (emphasis added). Applicant provides that one of several different possibilities is that the α11 and αmt are homologues or allelic variants with one or more amino acid differences. Such homologues or allelic variants would not destroy the novelty of the subject matter of the pending claims because they would not comprise an amino acid sequence identical to that of SEQ ID NO: 2.

However, the arguments of counsel cannot take the place of objective evidence in the record. *In re Schulze,* 145 USPQ 716, 718 (CCPA 1965).

The declaration filed under 37 CFR1.132 by Dr. Donald Gullberg on 11/21/05 is insufficient to over come the rejection under 35 U.S.C 102(b). Regarding the Examiner's evidentiary reference "the present data show that α11 integrin is identical with αmt", Dr. Gullberg declaration states this conclusion is based on the physical properties of the alpha subunits and their in vitro expression, not on their amino acid sequence (emphasis added by Dr. Gullberg). Dr. Gullberg declaration states that this is important because the polypeptides claimed in `403 application are limited by reference to their amino acid sequence, namely SEQ ID NO: 2 (see ¶8). Further, Dr. Gullberg declaration states that we have never been able to sequence the alpha-mt gene and determine the amino acid sequence of the encoded protein. In fact , to the best of my knowledge, the amino acid sequence of the alpha-mt subunit described in the Gullberg et al paper has never been determined (see ¶9). Dr. Gullberg declaration concluded that it is not possible to conclude that the alpha 11 subunit and the alpha-mt subunit are identical at the level of amino acid sequence (see ¶10). Said declaration further states that the Examiner's assertion that the amino acid sequence of SEQ ID NO: 2 is an inherent feature of the alpha-mt subunit is lacking scientific credibility (see ¶11). The declaration states that cloning of alpha-mt gene as described

in the Gullberg et al paper, from human fetal G6 myotubes did not succeed (see ¶12). Dr. Gullberg declaration concludes that given that we used a different source material for cloning the alpha-11 gene, it is impossible to conclude that the alpha-mt subunit disclosed in the Gullberg et al paper comprises an identical sequence to that of the alpha-11 subunit of the present application. Dr. Gullberg declaration provides one of several different possibilities, for example, that the alpha-11 and alpha-mt subunit are homologues or allelic variants with one or more amino acid differences. However, such homologues or allelic variants would not comprise an amino acid sequence identical to that shown in SEQ ID NO: 2 (see ¶13). Regarding Velling et al evidentiary reference, Dr. Gullberg declaration states that comparisons in this paper between the integrin alpha-mt subunit and the alpha-11 subunit described in the `403 application are bassed on the physical properties of the alpha subunits and their in vitro expression, not on their amino acid sequence. The declaration concludes that it cannot be concluded that the alpha-mt subunit comprises the amino acid sequence of SEQ ID NO:2.

While the Examiner acknowledges the possibilities presented by Dr. Gullberg declaration. However, Dr. Gullberg's declaration provided no evidence. Further, Applicant postdated publication arrived to the same scientific conclusion that α-mt is identical to the claimed α11 comprising the claimed SEQ ID NO: 2. In addition to Velling et al 1999 (of record), Tiger et al (Developmental Biology, 2001) teaches that α11β1 was first identified as a major integrin in cultured skeletal muscle cells (see page 117, 1st col., last ¶) citing Gullberg et al and Velling et al articles. Similarly, page 124, 2nd col., end full ¶) teaches that we originally identified α11 in myotube cultures for human fetal muscle cells and satellite cells also citing Gullberg et al and Velling et al articles. Therefore, the Examiner's conclusion that αmt is α11 is scientifically credible. Regarding the statement that αmt comes from different source material compared with α11. The Examiner notes that all human integrin receptor subunits derived from different human cell or tissue would have the same structural components irrespective of the starting material. Therefore, irrespective of the source material of the αmt and α11, based on the physical properties and characteristic of the αmt and α11 the skilled in the art would conclude that they are identical. Applicant's disclosure of SEQ ID NO:2 is mainly further characterization of otherwise old product. Regarding the possibility that αmt is homoloues or allelic variants, affidavits or Declaration are provided as evidence and must set forth facts, not merely conclusion. Dr. Gullberg declaration provided no scientific evidence that led to such conclusion. The evidence is to the contrary, αmt is identical to α11.

The declaration filed under 37 CFR1.132 by Dr. Teet Velling on 11/21/05 is insufficient to over come the rejection under 35 U.S.C 102(b). Dr. Velling declaration states that the experiments in the Velling et al paper correspond to the experiments described in the Examples section of the instant application no. 09/980,403 (see paragraph 7). Said declaration states that the Examiner has alleged that the alphamt subunit is "identical" to the alpha11 subunit since the Examiner has failed to define wha the means by the term "identical" (see paragraph 8). Dr. Velling declaration states that the basis of this comparison is highly significant because the alphamt subunit has never been sequenced. Dr. Velling declaration concluded that it is impossible to conclude that the alphamt subunit shares 100% sequence identity with the alpha11 subunit, this comparison has never been done (paragraph 9). Dr. Velling declaration further states that one could speculate

that the amino acid sequences of the alphamt subunit will be similar to the to the alpha11 subunit, based on the cloning strategy employed. However, it is simply not possible to say that the amino acid sequence are 100% identical. It is of Dr. Velling opinion that it is not even possible to say that 100% sequence identity between the alphamt subunit and the alpha11 subunit is probable since the two subunits were derived from different tissues. The alphamt subunit is derived from muscle cell precursors (myotubles) while the alpha11 subunit is cloned from a uterus cDNA library. It is quite possible that there will be a degree of sequence variation in such proteins expressed by different tissues. Also, it is of Dr. Velling opinion that the Examiner's objection based on Gullberg et al is lacking scientific basis.

While the Examiner acknowledges the possibilities presented by Dr. Velling declaration However, these opinions appear to be totally unsupported and uncorroborated, thus they cannot be considered reasoned opinions and are therefore simply allegations. Dr. Velling's statements that 100% sequence identity between the alphamt subunit and the alpha11 subunit is probable since the two subunits were derived from different tissues lacks the scientific basis because Dr. Velling did not provide evidence that α11 from different human tissue/cell has different structure component (i.e. not 100% identical). Further, it is noted that Dr. Velling's postdated publication has arrived to the same scientific conclusion as that of the Examiner, see Tiger et al, supra. Thus, faced with contradictory opinions of Dr. Velling regarding the identity of αmt, and lack of evidence that αmt is not 100% identical to α11, the declaration cannot be given much weight.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 23, 2006

Maher Haddad

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Continuation of Disposition of Claims: Claims pending in the application are 1-10,12,13,15-19,21,22,26,27,29-93,95-105,107-112,114,117,118,120,125,127-145,147,148 and 153-155.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-10,12,15-19,21,26,27,29-93,95-105,107-112,114,117,118,120,125,127-145,147 and 148.